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Accelerated Hypofractionated Radiation in Carcinoma Breast

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Abstract

Aim: Comparison of two different radiation fractionation schedules is done in post mastectomy breast cancer cases in relation to loco regional control, acute and late toxicities, survival and overall treatment time (O.T.T). The patient, tumor and treatment related parameters have also been studied.

Materials and Methods: Between December 2011 and December 2013, hundred patients of stage II to III carcinoma breast treated with surgery and chemotherapy received adjuvant radiation therapy with two different fractionation regimes:

- (Regimen-1, 50 patients) - 42.5 Gray/16 fractions/3.1 weeks @ 2.6 Gray/ fraction (#)
- (Regimen-2, 50 patients) - 50 Gray/25 fractions/5 weeks @ 2 Gray/fraction (#)

Assessment was done for loco regional and distant control rate, acute and late radiation toxicities, and quality of life related parameters.

Results: Maximum numbers of patients were of 40-50 year age, post-menopausal, with invasive ductal carcinoma of grade III and stage II or, III. Regimen 1 in comparison to Regimen 2 resulted in comparable loco regional and distant control rate. It also led to significantly less O.T.T. without any significant difference regarding acute and late radiation toxicities. It resulted in significant improvement in patient's quality of life parameters related to O.T.T.

Conclusion: In breast cancer patients undergoing post mastectomy radiotherapy, accelerated hypofractionated radiation (42.5 Gy/16 #/3.1 weeks) in comparison to the conventional radiotherapy (50 Gy/25#/5 weeks) results in comparable loco regional and distant control rates without any significant difference regarding acute and late radiation toxicities. It also leads to significant reduction in overall treatment time with significant improvement in patient's quality of life parameters related to O.T.T.

Key Message: Instead of protracted course of conventional radiotherapy (50 Gy/25#/5 weeks), use of high dose per fraction schedule with shorter duration of treatment (42.5 Gy/16 #/3.1 weeks) can be considered in PMRT patients as it is associated with comparable loco regional and distant control rates without any significant difference regarding acute and late radiation toxicities. The shorter fractionation schedule can especially be considered in radiotherapy setup of a developing country like ours which is already overloaded with such patients. It is also advantageous to the patient in terms of time, cost, comfort and acceptability as it significantly reduces the overall treatment time.

Keywords: Carcinoma breast, Post mastectomy radiotherapy (PMRT), Neoadjuvant chemotherapy, Radiation fractionation schedules

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Introduction

Breast cancer is the most common malignant neoplasm and a leading cause of death in women worldwide [1]. Breast carcinoma is treated with multimodal approach including surgery, chemotherapy, radiotherapy, hormonal therapy and immunotherapy [2]. Locoregional radiation therapy after modified radical mastectomy (MRM) not only significantly reduces locoregional recurrence rates but also leads to better survival outcome patients with high risk breast cancer [3-5]. Conventional course of radiation therapy {50 Gray (Gy) over 5 weeks} often leads to poor compliance of patients. Due to this long course, adjuvant treatment is sequenced so as to start radiation therapy after completion of adjuvant chemotherapy. Radiobiological models predict that ∞/ß ratio for breast cancer is low [2,3]. Tissues with low ∞/ß ratio have been shown to be more sensitive to the radiotherapy fraction size. Shorter over all treatment time is likely to have better control of clonogenic cell repopulation with improved loco regional control rates. Use of high dose per fraction schedule with shorter duration of treatment (accelerated hypofractionated radiotherapy) has shown comparable local control as well as quality of life to conventional radiotherapy without significant increase in treatment related toxicities.

Aims and Objectives

In this study, comparison of two different dose fractionation schedules of post mastectomy radiotherapy (PMRT) is done in terms of loco regional and distant control rate, acute and late radiation toxicities, overall treatment time and patient's quality of life parameters. The patient, tumor and treatment related parameters have also been studied.

Materials and Methods

This is an analysis of 100 patients with invasive, stage II or, III carcinoma breast that were treated by surgery, chemotherapy (neoadjuvant and/or adjuvant) and adjuvant radiation therapy between December 2011 and December 2013. All the patients are alive and are on regular follow up.

After meticulous work up, patients with stage II and stage III disease were included in our study. The patient's agreement and a written consent to participate in the study were taken. All the cases had to undergo an approval of the tumor board.

Inclusion criteria

1. Patients willing to participate in the study and also agreeing to come for regular follow up.
2. Biopsy proven carcinoma
3. Patient's age between 25-70 years
4. Good Karnofsky performance scale (>70%).
5. Stage II and III breast cancer
6. Any women with clinical/pathological tumor size ≥5 cm, or more than three positive axillary lymph nodes.
7. Surgery done for the tumor is modified radical mastectomy.
8. Radiography and chemotherapy naive patients
9. Time gap of three weeks to be maintained after completion of chemotherapy and subsequent start of radiation therapy
10. Interfield breast bridge separation not more than 25 cm.

Exclusion criteria

1. Karnofsky performance status (KPS) <70.
2. Co-morbid conditions; uncontrolled hypertension, diabetes mellitus or cardiac disease.
3. Connective tissue disorders like SLE etc.
4. Pregnant women.
5. Previous history of irradiation to chest wall.
6. Inoperable cases even after neoadjuvant chemotherapy.
7. Any surgery other than modified radical mastectomy.
8. Patients with distant metastasis.

All patients were treated with a continuous course of radiation therapy with once daily fractionation. They were treated 5 days a week from Monday to Friday. The fractionation regime was either:

- Accelerated Hypofractionated Schedule (Regimen-1) - 42.5 Gy/16 fractions/3.1 weeks @ 2.6 Gy/fraction
- Conventional Fractionation Schedule (Regimen-2) - 50 Gy/25 fractions/5 weeks @ 2 Gy/fraction

It was 2.6 Gy/fraction (Regimen-1) in 50/100 (50%) patients and 2 Gy/fraction (Regimen-2) in 50/100 (50%) patients.

Monitoring of the patients on radiotherapy

Acute toxicity was charted according to *RTOG Acute Radiation Morbidity Scoring Criteria*.

And late toxicity according to *RTOG/EORTC Late Radiation Morbidity Scoring Schema*

Arm edema was graded according to *LENT SOMA scale*.

For acute and late toxicity assessment, at least 7 parameters were noted and grading was done accordingly. The parameters were related to Skin, Subcutaneous tissue, Esophagus, Lung, Bone, Arm Edema & Restriction of shoulder joint movement (Grade 0 to IV). All the patients completed their planned treatment in stipulated time and none had to discontinue their treatment due to acute toxicity.

Follow up after treatment

Patients were followed up regularly at increasing intervals.

On each follow up patients were evaluated for:

- Loco Regional Control.
- Symptom and sign suggestive of distant metastasis.
- Late toxicity of radiation therapy.

Assessment of quality of life (QoL)

To assess it, we used *EORTC QoL* (European Organization Research and Treatment of Cancer – Quality of Life) questionnaire *(EORTC QLQ – BR23)* available for this purpose. In addition to these questionnaires, we added two more questions related to the impact of overall treatment time on their QoL.

Statistical analysis

Analysis was done using statistical tool SPSS 11.0. Two-tailed corrected chi-square test and unpaired *t*-test were used for p value calculation. The results were studied on an intention-to-treat basis.

Results and Observation

Pretreatment characteristics observed were as follows: The cardinal presenting symptom was lump in the breast. Most of the patients presented with progressively increasing painless or, slightly painful breast lump. The average duration of breast lump in all the patients was 6 months. Other important complaints included bloody nipple discharge, abnormal mammogram, skin changes in breast and axillary lymphadenopathy. Six patients were addicted to some kind of tobacco product. Patient related and tumor related parameters are detailed below in **Tables 1 and 2** respectively.

Outcome after radiotherapy

Follow up period of patients ranged from 6 months to 24 months with a median follow up of 15 months. Overall in our study, the local control rate was 92% with 8 out of 100 (8%) patients had clinically and pathologically proven chest wall recurrence. The regional axillary nodal failure was seen in 7 out of 100 patients (7%). The most common site of distant metastasis in both regimen groups was lung followed by bone.

The difference in incidence of local, regional nodal, and distant metastatic recurrence rate was nonsignificant between the two regimens.

Radiation related acute and late toxicities are detailed below in **Table 3**.

Overall treatment time (OTT)

The OTT for regimen 1 patients ranged from 21 to 24 (mean 22.5) days, while it was from 34 to 39 (mean 36.42) days for regimen-2 patients (p Value = 0.0001). Statistically this difference is considered to be extremely significant.

P value - 0.0001

T value - 47.69

Degree of freedom (df) - 98

Standard error of difference - 0.292

Quality of life (QoL) assessment

QoL related result is detailed below in **Table 4**. These results are based on below described questions asked to the patients.

Questions Asked to the Patients

01. Did you have any pain in your arm or shoulder?
02. Did you have a swollen arm or hand?
03. Was it difficult to raise your arm or to move it sideways?
04. Have you had any pain in the area of your affected breast?
05. Was the area of your affected breast swollen?
06. Was the area of your affected breast oversensitive?
07. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?
08. Did you feel physical or mental stress due to prolonged overall treatment time of radiotherapy?
09. Did you have economical problem due to prolonged treatment time?

Discussion

Surgery and radiotherapy are important for loco regional control in carcinoma breast [2,6].

Meta-analyses and Randomized Controlled Trials (at least 18 RCTs) of loco regional PMRT have consistently demonstrated that PMRT reduces the risk of loco regional failure by approximately two-thirds [5,7-14]. Later on, 3 large RCTs [5,11,12] and various meta-analyses [8-10,14,15] demonstrated that PMRT improves disease-free and overall survival. In our study, the loco regional control rate and overall locoregional control rate including salvage treatment at 2 years was 84% and 100% for regimen 1 group whereas it was 86% and 100% for regimen 2 group. Likewise the distant metastatic rate was 20% (10/50) in regimen 1 and 16% (8/50) in regimen 2. Regarding the locoregional recurrence rate our result was similar to the above mentioned studies. The distant metastatic rate in our study (18%) is much less than the above studies due to short period of follow-up and small number of patients included.

Data from randomized trials that compared hypofractionated radiation therapy with conventional radiation therapy, demonstrated no difference in late radiation morbidity or local recurrence [16-21]. A shorter fractionation schedule will lessen the burden of treatment for women, and will have important quality-of-life benefits with respect to convenience and less time away from home and work.

Regarding dose fractionation schedule of PMRT, there is no general agreement in literature [22-24]. The doses, ranging from 32.5 Gy/3 weeks to 60 Gy/10 to 14 weeks have been given [22-26]. It is not clear whether one fractionation scheme has any advantages over another [22-26].

Earliest report of fractionation in PMRT was by Kim et al., who compared four different fractionation schedules [27]. They found no difference in locoregional control rates as well as acute reactions in all four fractionation schedules.

Ragaz et al., successfully used 37.5 Gy/16Fr to chest wall at the

Table 1 Patient related characteristics.

Age Group	Regimen 1 (n = 50)		Regimen 2 (n = 50)		p Value
	No.	%	No.	%	
<30 Yr.	04	08	01	02	0.36
31-40 Yr.	10	20	08	16	0.8
41-50 Yr.	18	36	16	32	0.8
51-60 Yr.	12	24	18	36	0.27
>60 Yr.	06	12	07	14	0.7
Total	50	100	50	100	
Menopausal Status					
Premenopausal	14	28	09	18	0.34
Postmenopausal	18	36	25	50	0.2
Perimenopausal	14	28	12	24	0.8
Not Known	04	08	04	08	1.0
Total	50	100	50	100	
Parameter	Regimen 1 (n = 50)		Regimen 2(n = 50)		p Value
1. Age at 1st Childbirth	No. (%)		No. (%)		
<30 yrs.	48 (96%)		48 (96%)		1.0
>30 yrs.	02 (04%)		02 (04%)		1.0
2. Breast Feeding	No. (%)		No. (%)		
Present	48 (96%)		48 (96%)		1.0
Absent	02 (04%)		02 (04%)		1.0
3. H/O Benign Breast Disease	No. (%)		No. (%)		
Present	05 (10%)		04 (08%)		0.7
Absent	45 (90%)		46 (92%)		0.7
4. Family H/O Breast Cancer	No. (%)		No. (%)		
Present	02 (04%)		04 (08%)		0.67
Absent	48 (96%)		46 (92%)		0.67

rate of 234 cGy/Fr without significant acute or late sequelae [5].

Goel et al., compared 45 Gy/20 Fr/4 weeks versus 40 Gy/17 Fr/3.2 weeks in 108 patients of PMRT and found similar locoregional control rates as well as acute and late sequelae [28]. Whelan et al., randomized patients to receive whole breast irradiation of 42.5 Gy in 16 fractions over 22 days (short arm) or, 50 Gy in 25 fractions over 35 days (long arm) [16]. Five-year local recurrence-free, disease-free or overall survival rates were equivalent in both arms. The percentages of patients with an excellent or good global cosmetic outcome at 5 years were also equivalent. It concluded that the more convenient 22-day fractionation schedule appears to be an acceptable alternative to the 35-day schedule. A number of centers in Canada have already switched to this shorter fractionation course. Equal survival, local control, toxicity, and cosmetic outcomes at 5 years in the two arms with short fractionation (i.e., 16 fractions) after breast-conserving surgery have been reported in the recent *British Columbia Cancer Agency* randomized trials of aspirin versus no aspirin [17].

In our study, patients were treated by two regimens – conventional and accelerated hypofractionated. There was no significant difference between the two regimens regarding locoregional and distant failure rates, although there was significant difference in the overall treatment time. Patients in both the regimen groups tolerated the treatment well with nonsignificant difference in acute and late radiation toxicities. Our results are in consistent with the studies using accelerated hypofractionated radiotherapy in breast cancer.

Summary and Conclusion

Radiotherapy is an important component in management of post mastectomy breast cancer patients. Radiotherapy has major advantage in terms of high loco regional and distant control rate leading to improvement in disease free and overall survival. Use of high dose per fraction schedule with shorter duration of treatment (Regimen 1 – 42.5 Gy/16 #/3.1 weeks) in comparison to the protracted course of conventional radiotherapy (Regimen 2 – 50 Gy/25 #/5 weeks) resulted in comparable loco regional and distant control rate. The overall treatment time (O.T.T.) in Regimen 1 was significantly less in comparison to Regimen 2 without any significant difference regarding acute and late radiation toxicities of all the normal structures included in the radiation field (skin, subcutaneous tissue, esophagus, lung, bone, shoulder joint and arm oedema). Regimen 1 led to significant improvement in patient's quality of life parameters related to O.T.T. Shorter overall treatment time can be of great advantage in terms of time, cost, comfort and acceptability by the patients and it also reduces the heavy workload of already overburdened radiotherapy setup in a developing country like ours with scarcity of resources.

Table 2 Tumor related characteristics.

Involved Breast Quadrant	Regimen 1 (n = 50)		Regimen 2(n = 50)		p Value
	No. (%)		No. (%)		
Upper Outer	32 (64%)		30 (60%)		0.8
Central	08 (16%)		12 (24%)		0.45
Upper Inner	05 (10%)		03 (06%)		0.7
Lower Outer	04 (08%)		02 (04%)		0.67
Lower Inner	01(02%)		03 (06%)		0.6
Tumor Stage	**Regimen 1 (n = 50)**		**Regimen 2 (n = 50)**		**p Value**
	(No.)	(%)	(No.)	(%)	
IIB	07	14	05	10	0.7
IIIA	24	48	22	44	0.8
IIIB	17	34	20	40	0.67
Unknown	02	04	03	06	0.6
Total	50	100	50	100	
Histological Type	Regimen 1 (n = 50)		Regimen 2 (n = 50)		p Value
	No.	%	No.	%	
Ductal	41	82	43	86	0.78
Colloidal	02	04	01	02	0.5
Papillary	01	02	02	04	0.5
Lobular	06	12	04	08	0.7
Total	50	100	50	100	
Tumor Grade	Regimen 1 (n = 50)		Regimen 2 (n = 50)		p Value
	No.	%	No.	%	
Grade I	12	24	14	28	0.8
Grade II	20	40	16	32	0.5
Grade III	18	36	20	40	0.8
Total	50	100	50	100	
Receptor Status	Regimen 1 (n = 50)		Regimen 2 (n = 50)		p Value
	No.	%	No.	%	
ER (+)	25	50	30	60	0.4
ER (-)	20	40	16	32	0.5
PR (+)	10	20	05	10	0.26
PR (-)	35	70	41	82	0.2
Unknown	05	10	04	08	0.7
Total	50	100	50	100	

Table 3 Radiation Reaction Grading in Regimen 1 (n = 50) and Regimen 2 (n = 50).

Acute Radiation Reaction	Regimen 1 (n = 50) – No. (%)	Regimen 2 (n = 50) – No. (%)	p Value
Skin			
Grade 0	00 (0%)	00 (0%)	NS
Grade I	20 (40%)	27 (54%)	0.2
Grade II	27 (54%)	21 (42%)	0.3
Grade III	03 (06%)	02 (04%)	0.6
Subcutaneous Tissue			
Grade 0	00 (0%)	00 (0%)	NS
Grade I	25 (50%)	27 (54%)	0.8
Grade II	23 (46%)	22 (44%)	0.8
Grade III	02 (04%)	01 (02%)	0.5
Esophagus			
Grade 0	36 (72%)	40 (80%)	0.48
Grade I	10 (20%)	07 (14%)	0.6
Grade II	04 (08%)	03 (06%)	0.7
Grade III	00 (0%)	00 (0%)	NS
Lung			
Grade 0	42 (84%)	45 (90%)	0.5
Grade I	08 (16%)	05 (10%)	0.5
Grade II	00 (0%)	00 (0%)	NS
Grade III	00 (0%)	00 (0%)	NS
Shoulder Restriction			
Grade 0	39 (78%)	42 (84%)	0.6
Grade I	06 (12%)	03 (06%)	0.48
Grade II	04 (08%)	04 (08%)	1.0
Grade III	01 (02%)	01 (02%)	1.0
Arm Edema			
Grade 0	45 (90%)	46 (92%)	0.7
Grade I	01 (02%)	01 (02%)	1.0
Grade II	02 (04%)	02 (04%)	1.0
Grade III	02 (04%)	01 (02%)	0.5
Chronic Radiation Reaction	**Regimen 1 (n = 50) – No. (%)**	**Regimen 2 (n = 50) – No. (%)**	**p Value**
Skin			
Grade 0	03 (06%)	02 (04%)	0.6
Grade I	20 (40%)	26 (52%)	0.3
Grade II	25 (50%)	21 (42%)	0.5
Grade III	02 (04%)	01 (02%)	0.5
Subcutaneous Tissue			
Grade 0	02 (04%)	02 (04%)	1.0
Grade I	25 (50%)	28 (56%)	0.68
Grade II	20 (40%)	19 (38%)	0.8
Grade III	03 (06%)	01 (02%)	0.6
Esophagus			
Grade 0	33 (66%)	39 (78%)	0.26
Grade I	14 (28%)	09 (18%)	0.34
Grade II	03 (06%)	02 (04%)	0.6
Grade III	00 (0%)	00 (0%)	NS
Lung			
Grade 0	31 (62%)	37 (74%)	0.28
Grade I	10 (20%)	08 (16%)	0.79
Grade II	08 (16%)	05 (10%)	0.5
Grade III	01 (02%)	00 (0%)	0.06
Bone			
Grade 0	36 (72%)	42 (84%)	0.2
Grade I	10 (20%)	06 (12%)	0.4
Grade II	03 (06%)	02 (04%)	0.6
Grade III	00 (0%)	00 (0%)	NS
Grade IV	01 (02%)	00 (0%)	0.06
Shoulder Restriction			
Grade 0	25 (50%)	24 (48%)	0.8
Grade I	12 (24%)	13 (26%)	0.8
Grade II	08 (16%)	09 (18%)	0.8
Grade III	05 (10%)	04 (08%)	0.7
Arm Edema			
Grade 0	34 (68%)	36 (72%)	0.8
Grade I	08 (16%)	09 (18%)	0.8
Grade II	04 (08%)	02 (04%)	0.67
Grade III	04 (08%)	03 (06%)	0.7

Table 4 Comparison of the number and percentage of patients having QoL related problem in the two regimen group against the different questionnaires.

Question	Regimen 1 (n = 50)		Regimen 2 (n = 50)		p Value
	Number	Percentage	Number	Percentage	
01.	25	50	26	52	0.8
02.	16	32	14	28	0.8
03.	25	50	26	52	0.8
04.	32	64	30	60	0.8
05.	16	32	14	28	0.8
06.	15	30	12	24	0.6
07.	47	94	48	96	0.6
08.	32	64	45	90	**0.004**
09.	34	68	46	92	**0.006**

Question	Regimen 1 (n = 50)				Regimen 2 (n = 50)			
	Score1 (No.)	Score2 (No.)	Score3 (No.)	Score4 (No.)	Score1 (No.)	Score2 (No.)	Score3 (No.)	Score4 (No.)
01.	25	08	12	05	24	10	12	04
02.	34	05	07	04	36	05	06	03
03.	25	10	10	05	24	10	12	04
04.	18	12	14	06	20	12	13	05
05.	34	05	07	04	36	05	06	03
06.	35	06	07	02	38	04	07	01
07.	03	18	26	03	02	20	26	02
08.	18	12	12	08	05	19	20	06
09.	16	13	16	05	04	20	22	04

No: Number of patients

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